Original Paper

Clinical Utility of Serum Cystatin C in Predicting Diabetic Nephropathy Among Patients with Diabetes Mellitus: a Meta-Analysis

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Key Words

Diabetic nephropathy • Serum cystatin C • Glomerular filtration rate • Meta-analysis

Abstract

Background/Aims: Clinically, there is lack of predictors for diabetic nephropathy (DN) in diabetes mellitus (DM) without microalbuminuria, macroalbuminuria or retinopathy. **Methods:** PubMed, Chinese Biomedical Database, Cochrane Library, EMBASE and Elsevier Database were searched from inception to August 13, 2016. Studies involving patients with DM and containing data on cystatin C measurements and the measured glomerular filtration rate (mGFR) were included. Pooled sensitivity, specificity, positive predictive value, negative predictive value and other diagnostic indices were evaluated using a random effect model. **Results:** The meta-analysis enrolled 9 studies with 1417 patients. The pooled sensitivity and specificity of serum cystatin C for predicting DN were 0.88 (95% CI 0.85 - 0.91) and 0.85 (95% CI 0.82 - 0.87), respectively. The pooled positive and negative predictive values of serum cystatin C for predicting DN were 7.04 (95% CI 4.33 - 11.43) and 0.13 (95% CI 0.09 - 0.20), respectively. The area under the summary receiver operating characteristic (SROC) curve was 0.9549, and the diagnostic odds ratio was 66.80 (95% CI 27.92 - 159.86). **Conclusion:** Serum cystatin C is an early predictor of DN among patients with DM.

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Introduction

Diabetic nephropathy (DN) is one of the major chronic microvascular complications in diabetes mellitus (DM) and a leading cause of end-stage renal disease (ESRD), accounting for nearly half of all incident cases of ESRD in the developed world [1, 2]. In 2014, the American Diabetes Association (ADA) and the National Kidney Foundation (NKF) reached an agreement in which DN was referred to as the chronic kidney disease caused by DM, with a persistent estimated glomerular filtration rate (eGFR) of < 60 ml per min per 1.73 m^2 or a urinary albumin/creatinine ratio (ACR) of > 30 mg/g for more than 3 months [3]. The Joint Committee on Diabetic Nephropathy recommended the combination of the 24-hour albuminuria excretion rate (AER) and glomerular filtration rate (GFR) as the new classification of DN [4], and AER and spot ACR are considered the gold standard in diagnostic tests for DN [5]. Microscopically, DN is characterized by diffuse or nodular glomerulosclerosis, afferent and efferent hyaline arteriosclerosis, and tubulointerstitial fibrosis and atrophy [6].

The progression of DN is accompanied by a decrease in GFR among patients with DM. GFR and albuminuria have long been considered twin manifestations of DN [7]. However, research has shown that normoalbuminuric patients with DM may have significant renal damage [8, 9]. The Diabetes Control and Complications Trial (DCCT)/ Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that 24% of the examined DM patients with baseline eGFR level > 60 ml per min per 1.73 m^2 progressed to DN within one year; however, they did not experience microalbuminuria or macroalbuminuria [10]. Therefore, GFR is superior to AER or ACR in the early diagnosis of DN. Recently, serum cystatin C has been considered a new biomarker for the diagnosis of kidney damage. Several studies have shown that serum cystatin C is a better marker of decreased GFR than serum creatinine is [11-15].

In this study, we aimed to evaluate the GFR via serum cystatin C for the early detection of DN among DM patients. We conducted the meta-analysis to systematically analyze the relevant studies for determining the predictive value of serum cystatin C for the early detection of DN.

Materials and Methods

Data Sources and Search Strategy

The meta-analysis was performed according to the Observational Studies in Epidemiology (MOOSE) guidelines [16]. We performed a computerized search of PubMed (1966 to August 2016), Chinese Biomedical Database (1978 to August 2016), Cochrane Library (1900 to August 2016), EMBASE (1988 to August 2016) and Elsevier (2006 to August 2016), to identify potentially relevant articles. The medical subject headings (MeSH) were 'serum cystatin c' and 'diabetic nephropathy' AND 'glomerular filtration rate' AND (sensitivity OR specificity OR accuracy). The list of articles was reviewed by two authors (B-Q.Z. and H-H.Z.), who read the full text of all studies that were identified and determined their suitability for inclusion in the review, based on whether they met the pre-specified inclusion criteria. Reference lists of the identified articles were also reviewed manually to identify additional articles.

Study Selection

Two reviewers independently reviewed potentially relevant articles for eligibility and inclusion. Disagreement was resolved via discussion. Studies involving serum cystatin C predicting DN and giving the measured glomerular filtration rate (mGFR) for patients with DM were enrolled in this meta-analysis. There were no language or publishing date restrictions. The age of the subjects was not limited. Studies that involved patients with severe infection, diabetic ketoacidosis, heart failure, primary kidney disease, malignancy and drug-related renal damage were excluded. Studies that did not provide mGFR (sensitivity OR specificity OR accuracy) for patients were also excluded.

Fig. 1. Flow chart of study selection. DN, diabetic nephropathy; GFR, glomerular filtration rate; eGFR, measured glomerular filtration rate; mGFR, estimated glomerular filtration rate.

Data Extraction and quality assessment

Two independent researchers participated in the data extraction of the included studies. Disagreements about extracted data were resolved through discussion. The following variables were documented or recalculated: type of DM, measurement method of serum cystatin C, cut off value for serum cystatin C, specificity, sensitivity, and the area under the receiver operating characteristic curve (AUROC). Quality assessment, in each included study, was performed according to the quality assessment of studies diagnostic (QUADAS) document [17].

Table 1. Characteristics of the 9 studies include in the meta-analysis

Study (first author)	Country of origin	Sample size	Type of DN	cystatin C method	TP	FP	FN	TN	The method of GFR	Threshold of Serum cystatin C (mg/L)
Christensson AG ¹⁸	Sweden	123	Type 1 and 2	PETIA	14	3	1	105	⁵¹ Cr-EDTA	Not given
Beauvieux MC ¹⁹	France	124	Type 1 and 2	PENIA	70	6	6	42	⁵¹ Cr-EDTA	0.95
Rigalleau V ²⁰	France	124	Type 1 and 2	PENIA	70	9	6	39	⁵¹ Cr-EDTA	1.10
Iliadis F ²¹	Greece	448	Type 2	PETIA	118	61	27	242	⁵¹ Cr-EDTA	Not given
Bevc S ²²	Slovenia	113	Type 2	PENIA	73	0	13	27	⁵¹ Cr-EDTA	Not given
Oddoze C ²³	France	49	Not given	PENIA	9	4	1	35	⁵¹ Cr-EDTA	0.96
Chae HW ²⁴	Korea	113	Type 1 and 2	PENIA	17	31	3	62	creatinine	Not given
Bicik Z ²⁵	Turkish	72	Type 2	PETIA	29	4	3	36	creatinine	1.40
Macisaac RJ ²⁶	Austin	251	Type 1 and 2	PETIA	53	20	1	177	^{99m} Tc-DTPA	1.10

DN, diabetic nephropathy; TP, true positive; FP, false positive; FN, false negative; TN, true positive; GFR, glomerular filtration rate; PENIA, particle enhanced nephelometric immunoassay; PETIA, particle-enhanced turbidimetric immunoassay.

Statistical analysis

Statistical analysis was performed using the Meta-Disc 1.4 software. I^2 was used to examine the heterogeneity, with $I^2 > 50\%$ considered significant. If $I^2 > 50\%$, the random effects model was used for meta-analysis; otherwise, the random effects model was selected. The diagnostic test accuracy of serum cystatin C for detecting DN was expressed as the area under the summary receiver operating characteristic (SROC) curve.

Results

Search Results and Study Characteristics

The crude search initially yielded 101 articles. Of these, 78 were excluded after reading the abstracts and titles because they were review articles, animal studies, or irrelevant to the present analysis. We also read the potential relevant articles that were found by browsing the reference lists of the related articles and reviews and identified 5 additional articles eligible for our meta-analysis. After a careful and thorough screening process, we finally included 9 studies with a total of 1417 patients in the meta-analysis (figure 1). The characteristics of the included studies are listed in Table 1. All studies were published in English and represent international experiences from seven countries. Most studies were conducted in patients with type 2 DM. The detection methods of serum cystatin C included particle-enhanced turbidimetric immunoassay (PETIA) and particle enhanced nephelometric immunoassay (PENIA). GFR was laboratory obtained by testing the plasma clearance of ⁵¹Cr-EDTA [18-23], creatinine [24, 25] or ^{99m}Tc-DTPA [26]. Thresholds of serum cystatin C are listed in table 1.

Quality Assessments

QUADAS entries were adopted to improve the evaluation quality in the literature; each study is described with a "yes", "no", or "not clear" evaluation. The quality of the evaluation studies is shown in table 2. Four studies did not explain whether the target condition changed between the reference standard and index test [18-20, 23, 24].

Meta-analysis

Heterogeneity analysis. The heterogeneity of sensitivity was ($I^2 = 54.1\%$, $P = 0.0258$). The heterogeneity of specificity was ($I^2 = 86.3\%$, $P = 0.0000$). The heterogeneity of the positive likelihood ratio and negative likelihood ratio was ($I^2 = 84.2\%$, $P = 0.0000$) and ($I^2 = 50.2\%$, $P = 0.0414$), respectively. The heterogeneity of the diagnostic odds ratio (DOR) was ($I^2 = 71.6\%$, $P = 0.0005$).

Combined analysis. The analyses demonstrated that there was modest heterogeneity among the 7 studies. Our meta-analysis combined the effects using the random effects model.

Table 2. Quality assessment of the included studies (according to QUADAS)

Item	Yes	No	Unclear
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	(9)	(0)	(0)
2. Were selection criteria clearly described?	(9)	(0)	(0)
3. Is the reference standard likely to correctly classify the target condition?	(9)	(0)	(0)
4. Is the time period between reference standard and index test short enough to be reasonable sure that the target condition did not change between the two tests?	(4)	(0)	(5)
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	(9)	(0)	(0)
6. Did the patients receive the same reference standard regardless of the index result?	(9)	(0)	(0)
7. Was the reference standard independent of the index test. (i.e. the index test did not form part of the reference standard)?	(9)	(0)	(0)
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	(9)	(0)	(0)
9. Was the execution of the reference standard described in sufficient detail to permit its replication?	(9)	(0)	(0)
10. Were the index test results interpreted without knowledge of the results of the reference standard?	(0)	(0)	(9)
11. Were the reference standard results interpreted without knowledge of the results of the index test?	(0)	(0)	(9)
12. Were the same clinical data available when the test results were interpreted as would be available when the test is used in the practice?	(9)	(0)	(0)
13. Were uninterpretable/intermediate test results reported?	(0)	(0)	(9)
14. Were withdrawals from the study explained?	(0)	(0)	(9)

Fig. 2. Forest plots of pooled sensitivity of serum cystatin C for the estimation of glomerular filtration rate in predicting diabetic nephropathy. The red circles and horizontal lines represent the study-specific index of diagnosis and corresponding 95% CI, respectively. The diamond represents the pooled estimate with 95% CI.

Fig. 3. Forest plots of pooled specificity of serum cystatin C for the estimation of glomerular filtration rate in predicting diabetic nephropathy. The red circles and horizontal lines represent the study-specific index of diagnosis and corresponding 95% CI, respectively. The diamond represents the pooled estimate with 95% CI.

Forest plots of combined analyses are shown in figures 2-7. The sensitivity ranged from 0.81 to 0.98 (pooled sensitivity 0.88 95% CI 0.85, 0.91), while the specificity ranged from 0.67 to 1.00 (pooled specificity 0.85 95% CI 0.82, 0.87). The pooled positive likelihood ratio was 7.04 (95% CI 4.33, 11.43), while the negative likelihood ratio was 0.13 (95% CI 0.09, 0.20). DOR was 66.80 (95% CI 27.92, 159.86).

Fig. 4. Forest plots of pooled positive likelihood ratio of serum cystatin C for the estimation of glomerular filtration rate in predicting diabetic nephropathy. The red circles and horizontal lines represent the study-specific index of diagnosis and corresponding 95% CI, respectively. The diamond represents the pooled estimate with 95% CI.

Fig. 5. Forest plots of pooled negative likelihood ratio of serum cystatin C for the estimation of glomerular filtration rate in predicting diabetic nephropathy in diabetes disease. The red circles and horizontal lines represent the study-specific index of diagnosis and corresponding 95% CI, respectively. The diamond represents the pooled estimate with 95% CI.

Fig. 6. Forest plots of pooled Diagnostic OR of serum cystatin C for the estimation of glomerular filtration rate in predicting diabetic nephropathy. The red circles and horizontal lines represent the study-specific index of diagnosis and corresponding 95% CI, respectively. The diamond represents the pooled estimate with 95% CI.

SROC analysis

SROC for 9 studies, AUROC = 0.9549, Q-test* = 0.8972, SE (Q*) = 0.0224 figure 7.

Discussion

Serum cystatin C is a non-glycosylated, low molecular weight and basic protein that is produced at a steady rate and can be completely removed from the circulation by glomerular filtration, with subsequent proximal tubular reabsorption and degradation [27, 28]. Several studies have demonstrated that the levels of serum cystatin C are not affected by age,

Fig. 7. SROC curves of serum cystatin c for the estimation of glomerular filtration rate in predicting diabetic nephropathy in diabetes disease.

gender, and body mass and that its levels are not altered by inflammation conditions [28, 29] The progression of DN is accompanied by a decrease in GFR among patients with DM. As the patient's GFR falls below 60 ml/min/1.73 m², there is an increased risk of death and cardiovascular mortality [30]. The present meta-analysis aimed to compare serum cystatin C with mGFR to predict DN.

The present meta-analysis enrolled 9 studies referring to the serum cystatin C test for the early prediction of DN. The results showed that the pooled sensitivity and specificity for detecting DN with the serum cystatin C were 0.88 and 0.85, respectively. The higher the positive likelihood ratio was, the greater the value of the diagnosis of disease was, whereas the smaller the negative likelihood ratio was, the lower the possibility was of suffering from the specific disease. Hence, it may be more appropriate to consider the likelihood ratio when explaining the results. The pooled positive likelihood ratio was 7.04, which showed that DM patients with elevated serum cystatin C were more likely to progress to DN. The pooled negative likelihood ratio was 0.13, which showed that patients with normal serum cystatin C had fewer incidents of DN. Additionally, the SROC curve was an overall evaluation of the value of the diagnostic tests. The present meta-analysis showed that the SROC area under the curve was 0.9549 and that the Q value was 0.8972. DOR is the ratio of the true positives to false positives compared to the ratio of the true negatives to false negatives. The diagnostic odds ratio was 66.80. Therefore, cystatin C is a more reliable predictor of DN among patients with DM.

The source of heterogeneity could be explained by the following limitations. There were three methods of measuring GFR. First, although most of the methods for measuring GFR in the studies used the ⁵¹Cr-EDTA plasma clearance, the observation time was different. Second, most studies did not give the diagnostic criteria of diabetes.

Our analysis has several limitations. For instance, we did not consider the effects of different methods for detecting the concentration of cystatin C. Several collaborative works have shown comparative performances between the nephelometric and turbidimetric immunoassay methods [31-33] to eGFR, but the results are different. Leeflang *et al.* suggested that we should consider the paired nature of the estimates and their dependence on the threshold [34]. In this article, many studies did not report the diagnostic value of serum

cystatin C [18, 21, 22, 24], but the difference of the analysis of diagnostic threshold was not significant ($p = 0.4796$). Clinical settings and study populations that were different, such as by racial or ethnic group, may explain the cut-off value used in these studies. The subjects represented seven countries. Hence, it may be necessary for each center to have different serum cystatin C cut off-values for each clinical setting.

Recently, Amini S demonstrated that among Kurdish patients, DN patients with a high frequency of CC genotype of solute carrier family 2 facilitated glucose transporter member 1 (SLC2A1) T20882C (HaeIII) polymorphism compared with diabetic patients without DN. This study also revealed that the C allele of SLC2A1 HaeIII polymorphism was associated with higher cystatin C and eGFR, but there was no relationship between HaeIII polymorphism and glycosylated hemoglobin (HbA1c) or between fasting blood glucose (FBG) and microalbuminuria [35]. Vaidya VS et al showed that tubular dysfunction is an important component of the early course of DN [36]. Arun O showed that serum cystatin C values may indicate acute kidney injury (AKI) signs earlier than blood urea nitrogen and serum creatinine in DM patients undergoing Coronary Artery Bypass Graft Surgery [37]. The study by Ozturk SA et al. indicated that the lower cystatin C levels in Wistar Albino rats that were given pneumoperitoneum and theophylline are suggestive of lower renal injury [38].

Conslusion

In conclusion, the current article shows that serum cystatin C is a significant predictor of DN among patients with DM and that the cystatin C test is more economical and more convenient than the standard method for GFR. With the development of medical treatment level, DN remains a therapeutic challenge with major diabetic complications [39]. The early detection of DN is very important and can improve patient outcomes.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

References

- 1 Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, Hirsch IB, Kalantar-Zadeh K, Narva AS, Navaneethan SD, Neumiller JJ, Patel UD, Ratner RE, Whaley-Connell AT, Molitch ME: Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care* 2014;37:2864-2883.
- 2 Nakai S, Iseki K, Itami N, Ogata S, Kazama JJ, Kimata N, Shigematsu T, Shinoda T, Shoji T, Suzuki K, Taniguchi M, Tsuchida K, Nakamoto H, Nishi H, Hashimoto S, Hasegawa T, Hanafusa N, Hamano T, Fujii N, Masakane I, Marubayashi S, Morita O, Yamagata K, Wakai K, Wada A, Watanabe Y, Tsubakihara Y: An overview of regular dialysis treatment in Japan (as of 31 December 2010). *Ther Apher Dial* 2012;16:483-521.
- 3 Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, Hirsch IB, Kalantar-Zadeh K, Narva AS, Navaneethan SD, Neumiller JJ, Patel UD, Ratner RE, Whaley-Connell AT, Molitch ME: Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care* 2014 Oct;37:2864-2883.
- 4 Haneda M, Utsunomiya K, Koya D, Babazono T, Moriya T, Makino H, Kimura K, Suzuki Y, Wada T, Ogawa S, Inaba M, Kanno Y, Shigematsu T, Masakane I, Tsuchiya K, Honda K, Ichikawa K, Shide K; Joint Committee on Diabetic Nephropathy: A new Classification of Diabetic Nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy. *J Diabetes Investig* 2015;6:242-246.
- 5 Kowalski A, Krikorian A, Lerma EV: Diabetes and chronic kidney disease. *Dis Mon* 2015;61:378-386.

- 6 Alsaad KO, Herzenberg AM: Distinguishing diabetic nephropathy from other causes of glomerulosclerosis: an update. *J Clin Pathol* 2007;60:18-26.
- 7 de Boer IH, Steffes MW: Glomerular filtration rate and albuminuria: twin manifestations of nephropathy in diabetes. *J Am Soc Nephro* 2007;18:1036-1037.
- 8 Caramori ML, Fioretto P, Mauer M: Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: an indicator of more advanced glomerular lesions. *Diabetes* 2003;52:1036-1040.
- 9 MacIsaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeil KJ, Jerums G: Nonalbuminuric renal insufficiency in type 2 diabetes. *Diabetes Care* 2004;27:195-200.
- 10 Molitch ME, Steffes M, Sun W, Rutledge B, Cleary P, de Boer IH, Zinman B, Lachin J; Epidemiology of Diabetes Interventions and Complications Study Group: Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. *Diabetes Care* 2010;33:1536-1543.
- 11 Newman DJ, Thakkar H, Edwards RG, Wilkie M, White T, Grubb AO, Price CP: Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. *Kidney Int* 1995;47:312-318.
- 12 Bevc S, Hojs R, Ekar R, Gorenjak M, Puklavec L: Simple cystatin C formula compared to serum creatinine-based formula for glomerular filtration rate in patients with mildly to moderately impaired kidney function. *Kidney Blood Press Res* 2012;35:649-654.
- 13 Mussap M, Dalla Vestra M, Fioretto P, Saller A, Varagnolo M, Nosadini R, Plebani M: Cystatin C is a more sensitive marker than creatinine for the estimation of GFR in type 2 diabetic patients. *Kidney Int* 2002;61:1453-1461.
- 14 Perlemoine C, Beauvieux MC, Rigalleau V, Baillet L, Barthes N, Derache P, Gin H: Interest of cystatin C in screening diabetic patients for early impairment of renal function. *Metabolism* 2003;52:1258-1264.
- 15 Pucci L, Triscornia S, Lucchesi D, Fotino C, Pellegrini G, Pardini E, Miccoli R, Del Prato S, Penno G: Cystatin C and estimates of renal function: searching for a better measure of kidney function in diabetic patients. *Clin Chem* 2007;53:480-488.
- 16 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB: Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-2012.
- 17 Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J: The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003;3:25.
- 18 Christensson AG, Grubb AO, Nilsson JA, Norrgren K, Sterner G, Sundkvist G: Serum cystatin C advantageous compared with serum creatinine in the detection of mild but not severe diabetic nephropathy. *J Intern Med* 2004;256:510-518.
- 19 Beauvieux MC, Le Moigne F, Lasseur C, Raffaitin C, Perlemoine C, Barthe N, Chauveau P, Combe C, Gin H, Rigalleau V: New predictive equations improve monitoring of kidney function in patients with diabetes. *Diabetes Care* 2007;30:1988-1994.
- 20 Rigalleau V, Beauvieux MC, Le Moigne F, Lasseur C, Chauveau P, Raffaitin C, Perlemoine C, Barthe N, Combe C, Gin H: Cystatin C improves the diagnosis and stratification of chronic kidney disease, and the estimation of glomerular filtration rate in diabetes. *Diabetes Metab* 2008;34:482-489.
- 21 Iliadis F, Didangelos T, Ntemka A, Makedou A, Moravidis E, Gotzamani-Psarakou A, Kouloukourgiotou T, Grekas D: Glomerular filtration rate estimation in patients with type 2 diabetes: creatinine- or cystatin C-based equations? *Diabetologia* 2011;54:2987-2994.
- 22 Bevc S, Hojs R, Ekar R, Završnik M, Gorenjak M, Puklavec L: Simple cystatin C formula for estimation of glomerular filtration rate in overweight patients with diabetes mellitus type 2 and chronic kidney disease. *Exp Diabetes Res* 2012;2012:179849.
- 23 Oddo C, Morange S, Portugal H, Berland Y, Dussol B: Cystatin C is not more sensitive than creatinine for detecting early renal impairment in patients with diabetes. *Am J Kidney Dis* 2001;38:310-316.
- 24 Chae HW, Shin JI, Kwon AR, Kim HS, Kim DH: Spot urine albumin to creatinine ratio and serum cystatin C are effective for detection of diabetic nephropathy in childhood diabetic patients. *J Korean Med Sci* 2012;27:784-787.

- 25 Bicik Z, Bahcebasi T, Kulaksizoglu S, Yavuz O: The efficacy of cystatin C assay in the prediction of glomerular filtration rate. Is it a more reliable marker for renal failure? *Clin Chem Lab Med* 2005;43:855-861.
- 26 Macisaac RJ, Tsalamandris C, Thomas MC, Premaratne E, Panagiotopoulos S, Smith TJ, Poon A, Jenkins MA, Ratnaik SL, Power DA, Jerums G: The accuracy of cystatin C and commonly used creatinine-based methods for detecting moderate and mild chronic kidney disease in diabetes. *Diabet Med* 2007;24:443-448.
- 27 Newman DJ, Thakkar H, Edwards RG, Wilkie M, White T, Grubb AO, Price CP: Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. *Kidney Int* 1995;47:312-318.
- 28 Bökenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodehl J: Cystatin C--a new marker of glomerular filtration rate in children independent of age and height. *Pediatrics* 1998;101:875-881.
- 29 Javanmardi M, Azadi NA, Amini S, Abdi M: Diagnostic value of cystatin C for diagnosis of early renal damages in type 2 diabetic mellitus patients: The first experience in Iran. *J Res Med Sci* 2015;20:571-576.
- 30 Ekart R, Bevc S, Hojs N, Knehtl M, Dvoršak B, Hojs R: Albuminuria is Associated With Subendocardial Viability Ratio in Chronic Kidney Disease Patients. *Kidney Blood Press Res* 2015;40:565-574.
- 31 Sunde K, Nilsen T, Flodin M: Performance characteristics of a cystatin C immunoassay with avian antibodies. *Ups J Med Sci* 2007;112:21-37.
- 32 Hossain MA, Emara M, El Moselhi H, Shoker A: Comparing measures of cystatin C in human sera by three methods. *Am J Nephrol* 2009;29:381-391.
- 33 Finney H, Newman DJ, Gruber W, Merle P, Price CP: Initial evaluation of cystatin C measurement by particle-enhanced immunonephelometry on the Behring nephelometer systems (BNA, BN II). *Clin Chem* 1997;43:1016-1022.
- 34 Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM; Cochrane Diagnostic Test Accuracy Working Group: Systematic reviews of diagnostic test accuracy. *Ann Intern Med* 2008;149:889-897.
- 35 Amini S, Javanmardi M, Mokarizadeh A, Maroofi F, Jalali C, Azadi NA, Mohammadi H, Abdi M: Association of HaeIII single nucleotide polymorphisms in the SLC2A1 gene with risk of diabetic nephropathy; evidence from Kurdish patients with type 2 diabetes mellitus. *QJM* 2016;109:399-404.
- 36 Vaidya VS, Niewczas MA, Ficociello LH, Johnson AC, Collings FB, Warram JH, Krolewski AS, Bonventre JV: Regression of microalbuminuria in type 1 diabetes is associated with lower levels of urinary tubular injury biomarkers, kidney injury molecule-1, and N-acetyl-β-D-glucosaminidase. *Kidney Int* 2011;79:464-470.
- 37 Arun O, Celik G, Oc B, Unlu A, Celik JB, Oc M, Duman A: Renal effects of coronary artery bypass graft surgery in diabetic and non-diabetic patients: a study with urinary neutrophil gelatinase-associated lipocalin and serum cystatin C. *Kidney Blood Press Res* 2015;40:141-152.
- 38 Ozturk SA, Ceylan C, Serel TA, Doluoglu OG, Soyupek AS, Guzel A, Özorak A, Uz E, Savas HB, Baspinar S: Protective effect of theophylline on renal functions in experimental pneumoperitoneum model. *Ren Fail* 2015;37:1044-1049.
- 39 Vukovic I, Bozic J, Markotic A, Ljubicic S, Ticinovic Kurir T: The missing link - likely pathogenetic role of GM3 and other gangliosides in the development of diabetic nephropathy. *Kidney Blood Press Res* 2015;40:306-314.